IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Franklin H. Portugal — Examiner: J. Souaya

Serial NO:: 09/027,439 — Group Art Unit: 1634

Filed: February 20, 1998

Title: COMPOSITIONS AND METHODS FOR DIFFERENTIATING AMONG SHIGELLA SPECIES AND SHIGELLA FROM E. COLI SPECIES

BRIEF ON APPEAL

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal filed August 1, 2003, attached herewith are three copies of Appellants Brief on Appeal and a check for the statutory fee of $165.00 is enclosed.

(I) Real Parties in Interest

The real parties in interest are Franklin H. Portugal and Cabtech Inc, both of 9105 Fall River Lane, Potomac MD 20854. This is not reflected in the assignment records. An assignment from three of the four originally named inventors to the University of Maryland System, is of record. On May 17, 2001, the University of Maryland gave notice to these inventors that the University's rights in the invention would be transferred to Cabtech , Inc (see attachment B).

(II) Related Appeals and Interferences

There are no appeals or interferences known to Appellant or Appellant's legal representative which will be directly effected by or have any bearing on the Boards decision in

the pending appeal.

(III) Status of the Claims

Claims 21-36, 47, 48, and 52-58 are pending in this application and are attached hereto as Appendix A. Claims 21-36 are withdrawn from consideration. Claims 47, 48 and 53-38 are rejected and are the subject of this Appeal. Claim 52 has been allowed.

(IV) Status of Amendments After Final

An amendment after final has been submitted simultaneously with this Brief on Appeal. The remarks herein and the Appendix attached hereto address the claims without these amendments. Should any or all of the amendments made after final be entered, certain issues will become moot and the appendix inaccurate. If issues remain, a new Appendix will be provided and a Supplemental Brief will be filed.

(V) Summary of the Invention

The invention claimed relates to nucleic acid molecules such as probes used to discriminate between *Shigella* and *E-coli* bacteria and allow identification of *Shigella* species present in a test sample. The application includes claims directed to isolated nucleic acid molecules of SEQ ID NOS: 3, 4, 5 and 6, RNA equivalents thereof, and nucleic acids complementary to these isolated molecules. The application also includes claims to probes (claims 55-58) which target *Shigella flexneri, Shigella sonnei, Shigella dysenteriae, or Shigella boydii*. The probes comprise (or consist of) a fragment of more than 10 bases in length, up to 40 bases in length of nucleotide sequence SEQ ID NO: 3, 4, 5 or 6, or RNA equivalents thereof or nucleic acids complementary thereto.

(VI) Issues

1. Whether the disclosure satisfies the requirements of 37 C.F.R. §1.821(d).
2. Whether claim 58 satisfies the requirements of 37 C.F.R. §1.75(c).
3. Whether claims 55-58 define statutory subject matter and satisfy the requirements

of 35 U.S.C §101.

4. Whether claims 55-58 are sufficiently definite to satisfy the requirements of 35 U.S.C §112, second paragraph.
5. Whether claims 47, 48, 53 and 55-58 are anticipated by Hogan (U.S. Patent NO: 5,541,308).
6. Whether claim 54 is anticipated by Brennan, et. al. (U.S. Patent NO: 5,474,796).
7. Whether claims 47, 48, 53 and 55-58 are anticipated by Chembank Accession NOS: X96964 or X80726 disclosed in Cilia, et. al..
8. Whether claims 47, 48, 53 and 55-58 are obvious in view of Accession NO: A14565 in view of Dyson (New Jersey) Essential Molecular Biology, Vol. II: A Practical Approach, chapter 5, pages 111-156, Brown, T.A. Ed., Oxford Press, Oxford, 1992.

(VII) Grouping of Claims

The claims herein do not stand or fall together with respect to any of the above issues.

(VIII) Arguments

Issue I: Whether the disclosure satisfies the requirements of 37 C.F.R. §1.821(d).

Appellants maintain the specification conforms to the requirements of 37 C.F.R. §1.184(d) which is repeated below.

> d) Where the description or claims of a patent application discuss a sequence that is set forth in the ''Sequence Listing'' in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by ''SEQ ID NO:'' in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

The sequences referred to in Table II are preceded by SEQ ID NOS: for their first occurrence. This satisfies the literal requirements of the rule. The rule does not require SEQ ID NOS: be repetitively provided in each instance that reference is made to a sequence in the sequence listing. Inserting the additional SEQ ID NOS: here does not help one skilled in the art

to understand the invention. The sequences are clearly identified by comparison to a preceding sequence with a SEQ ID NO:

Issue II: Whether claim 58 satisfies the requirements of 37 C.F.R. §1.75(c).

Appellants maintain claim 58 does further limit the subject matter of claim 56, the claim upon which it depends. As a dependent claim, claim 58 must be construed to incorporate all the limitations of claim 56, including the limitation that the probe defined consists of a fragment from greater than 10 bases in length to 40 bases in length of a nucleotide sequence of SEQ ID NOS: 3, 4, 5 or 6. The term "comprises 15-25 bases in length" serves to modify this range. It cannot expand the scope of the range to encompass probes longer than those defined in claim 56. The claim further limits the subject matter of claim 56 in defining probes with a minimum of 15 bases in length.

Issue III: Whether claims 55-58 define statutory subject matter and satisfy the requirements of 35 U.S.C §101.

Appellants maintain claims 55-58 do define statutory subject matter under 35 U.S.C §101 repeated below.

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 55-58 define probes which are compositions of matter which are useful as investigative tools and clearly fall within the subject matter defined by the statute. The rejection is based on the allegation that the claims define subject matter found in nature. No evidence has been presented that these probes exist in nature. Where a molecule used as a probe is found in nature, it is relevant as prior art under 35 U.S.C. §§102 and 103. No evidence has been presented that any of the probes claimed are anticipated or obvious based on full nucleic acid sequences found in nature.

Issue IV: Whether claims 55-58 are sufficiently definite to satisfy the requirements of 35 U.S.C §112, second paragraph.

Appellants maintain that claims 55-58 are sufficiently definite to particularly point out and distinctly claim the subject matter which Applicant regards as the invention, and thus satisfy the requirements of 35 U.S.C §112, second paragraph. The Examiner objects to the phrase "greater than 10-40 bases in length" and alleges it is not clear if a nucleic acid of 15 bases in length would meet the limitations. While Appellants admit the language is not conventional, this language can only be interpreted to define a range having a lower limit of greater than 10 bases in length , i.e. 11 bases in length, and an upper limit of 40 bases in length. Therefore, this language is not indefinite. Such an interpretation is even more certain in view of the disclosure within the specification that appears on page 16, where fragments "between about 10 and about 40 nucleotides" are said to "generally find use in hybridization embodiments." Here the range is said to include "10", therefore one skilled in the art would recognize "greater than 10" would encompass a nucleic acid of 15 bases. Therefore, with or without reference to the specification, claims 55-58 satisfy the requirements of 35 U.S.C §112, second paragraph.

Issue V: Whether claims 47, 48, 53 and 55-58 are anticipated by Hogan (U.S. Patent NO: 5,541,308).

Appellants maintain claims 47, 48, 53 and 55-58 are not anticipated by the disclosure within U.S. Patent NO: 5,541,308 issued to Hogan. It is alleged that Hogan teaches a probe which has complementary sequences of portions of SEQ ID NO: 3, 4, 5 and 6. Appellants maintain providing a complementary sequence to only a portion of SEQ ID NOS: 3, 4, 5 and 6 does not anticipate claims 47, 48, 53 or 55-58.

Issue VI: Whether claim 54 is anticipated by Brennan, et. al. (U.S. Patent NO: 5,474,796).

The Examiner has interpreted claim 54 to encompass fragments of SEQ ID. NOS: 3, 4,5, and 6. Appellants agree with this interpretation and have amended claim 54 in the Amendment After Final to replace the word "a" with the word "the".

Issue VII: Whether claims 47, 48, 53 and 55-58 are anticipated by Chembank Accession NOS: X96964 or X80726 disclosed in Cilia, et. al..

Claims 47, 48, 53 and 55-58 are rejected on the basis that the complementary sequence of SEQ ID NO: 4 is allegedly anticipated by the disclosure by Cilia et al of the sequences of Accession NOS: X96964 or X80726. As the examiner acknowledges, the accession numbers do not recite the complement and therefore, they cannot anticipate any of the complementary sequences claimed herein.

Issue VIII: Whether claims 47, 48, 53 and 55-58 are obvious in view of Accession NO: A14565 in view of the Dyson Publication

These combined teachings do not show or suggest SEQ ID NOS: 3, 4, 5 or 6 and therefore they do not show or suggest their complements (capable of base-pairing according to the standard Watson-Crick complementarity rules) or their substantial complements capable of hybridizing under the conditions specified in the claim. The Examiner has interpreted the recitation of "complement capable of base-pairing according to the standard Watson-Crick complementarity rules" to not require completely complementary sequences although this is clearly intended in that the claim defines substantially complementary sequences. The recitations would be redundant if both defined complementary sequences which were not complete. Appellant submits there is no evidence it would be obvious to prepare a sequence completely complementary or substantially complementary to SEQ ID NOS: 3,4,5 or 6 and therefore, these claims have not been shown to be prima-facie obvious.

Regardless of the scope of the terms "complementary" and "substantially complementary", the references do not disclose complementary sequences of the accession numbers described and no evidence of motivation to prepare such complementary sequences has

been presented. The examiner relies on hindsight to reconstruct Appellant's invention, which cannot properly support a rejection, under 35 U.S.C. §103.

(IX) Conclusion

For the reasons stated above, Appellants respectfully submit the subject matter of the pending claims is novel and unobvious over the cited references and the specification in claims satisfy the requirements of 35 U.S.C §112, first and second paragraph. Therefore, Appellants respectfully request the outstanding rejections be reversed.

Respectfully submitted,

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Attorney Docket NO:: CABTEC-2

Date: November 3, 2003

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APPENDIX

21. (Withdrawn) A method for testing an unknown sample suspected of having *E. coli* or *Shigella* species presence comprising

demonstrating an identifying nucleotide or identifying combination of nucleotides of 16s rRna or 16s rDNA as set forth in Table 2 within the sample

wherein the demonstration of an identifying nucleotide or identifying combination of nucleotides establishes presence or absence of *E. coli* or *Shigella* in the sample.

22. (Withdrawn) The method of claim 21 wherein the demonstrating is by a method selected from the group consisting of direct sequencing, dot blot hybridization, solution hybridization, Northern blotting, and Southern blotting of the unknown sample.

23. (Withdrawn) The method of claim 21 wherein the unknown sample is suspected of containing *E. coli* and the identifying nucleotide is a T at position 88p.

24. (Withdrawn) The method of claim 21 wherein the unknown sample is suspected of containing *Shigella sonnei* and the identifying nucleotide is a C at position 964, or a deletion at position 978.

25. (Withdrawn) The method of claim 21 wherein the unknown sample is suspected of containing *Shigella dysenteriae* and the identifying nucleotide is an A at position 76.

26. (Withdrawn) The method of claim 21 wherein the unknown sample is suspected of containing *Shigella boydii* and the identifying nucleotide is a C at position 92.

27. (Withdrawn) The method of claim 21 wherein the unknown sample is suspected of containing *Shigella flexneri* and the identifying nucleotide is a G nucleotide at position 79 in combination with a G at position 89 or a C at position 92p.

28. (Withdrawn) The method of claim 21 wherein the unknown sample is a clinical sample for diagnosis.

29. (Withdrawn) The method of claim 21 wherein the unknown sample is a food sample.

30. (Withdrawn) The method of claim 21 wherein the unknown sample is an environmental sample.

31. (Withdrawn) An assay kit for distinguishing *Shigella* from *E. coli* comprising the purified nucleic acid molecule of claim 11 packaged in at least one container.

32. (Withdrawn) An assay kit for distinguishing *E. coli* from *Shigella* comprising the purified nucleic acid molecule of claim 12 packaged in at least one container.

33. (Withdrawn) An assay kit for identifying *Shigella sonnei* comprising the purified nucleic acid molecule of claim 14 packaged in at least one container.

34. (Withdrawn) An assay kit for identifying *Shigella flexneri* comprising the combination of nucleic acid molecules of claim 18 packaged in at least one container.

35. (Withdrawn) An assay kit for identifying *Shigella boydii* comprising the purified nucleic acid molecules of claim 16 packaged in at least one container.

36. (Withdrawn) An assay kit for identifying *Shigella dysenteriae* comprising the purified nucleic acid molecule of claim 15 packaged in at least one container.

47. An isolated nucleic acid molecule comprising SEQ ID NO: 3, SEQ ID NO:. 4, SEQ ID NO: 5, or SEQ ID NO: 6,

or an RNA equivalent thereof,

or a nucleic acid complementary to said isolated molecule , capable of base-pairing according to the standard Watson-Crick complementarity rules,

or a nucleic acid substantially complementary to said isolated molecule which is capable of hybridizing to the nucleic acid molecule under the following stringent conditions:

hybridization at 40°-65 °C for 14-16 hours in a hybridization solution at ph 7.8,

containing 0.9 M NaCl, 0.12 M Tris-HCl, 6nM EDTA, 0.1M sodium phosphate buffer,

0.1% SDS and 0.1% polyvinylpyrrolidone,

followed by three 15-minute washes at 40°-65 °C to remove unbound probes in a solution at pH 7, containing 0.075 M NaCl, 0.0075 M Na Citrate and 0.1% SDS.

48. An isolated nucleic acid molecule consisting of

SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6,

or an RNA equivalent thereof,

or a nucleic acid complementary to said isolated molecule , capable of base-pairing according to the standard Watson-Crick complementarity rules,

or a nucleic acid substantially complementary to said isolated molecule which is capable of hybridizing to the nucleic acid molecule under the following stringent conditions:

hybridization at 40°-65 °C for 14-16 hours in a hybridization solution at ph 7.8, containing 0.9 M NaCl, 0.12 M Tris-HCl, 6nM EDTA, 0.1M sodium phosphate buffer, 0.1% SDS and 0.1% polyvinylpyrrolidone,

followed by three 15-minute washes at 40°-65 °C to remove unbound probes in a solution at pH 7, containing 0.075 M NaCl, 0.0075 M Na Citrate and 0.1% SDS.

52. The isolated nucleic acid molecule consisting of the nucleotide sequence of SEQ ID NO: 6.

53. An isolated nucleic acid molecule comprising a nucleotide sequence of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, or SEQ ID NO: 6,

or an RNA equivalent thereof;

or a nucleic acid complementary to said isolated molecule, capable of base-pairing according to the standard Watson-Crick complementarity rules .

54. (Previously Presented) An isolated nucleic acid molecule consisting of a nucleotide sequence of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5 or SEQ ID NO: 6 or an RNA equivalent thereof.

55. (Currently Amended) An isolated ~~A~~ probe which

a) targets *Shigella flexneri* comprising a fragment greater than 10 to 40 bases in length of a nucleotide sequence SEQ ID NO: 3, an RNA equivalent thereof, or a nucleic acid complementary to said molecule, capable of base-pairing according to the standard Watson-Crick complementarity rules,

b) targets *Shigella sonnei* comprising a fragment greater than 10 to 40 bases in length of a nucleotide sequence SEQ ID NO: 4, an RNA equivalent thereof, or a nucleic acid complementary to said molecule, capable of base-pairing according to the standard Watson-Crick complementarity rules,

c) targets *Shigella dysenteriae* comprising a fragment greater than 10 to 40 bases in length of a nucleotide sequence SEQ ID NO: 5, an RNA equivalent thereof, or a nucleic acid complementary to said molecule,capable of base-pairing according to the standard Watson-Crick complementarity rules,

or

d) targets *Shigella boydii* comprising a fragment greater than 10 to 40 bases in length of a nucleotide sequence SEQ ID NO: 6, an RNA equivalent thereof, or a nucleic acid complementary

to said molecule, capable of base-pairing according to the standard Watson-Crick complementarity rules.

56. (Currently Amended) A probe which

a) targets *Shigella flexneri* consisting of a fragment greater than 10 to 40 bases in length of a nucleotide sequence SEQ ID NO: 3, an RNA equivalent thereof, or a nucleic acid complementary to said molecule, capable of base-pairing according to the standard Watson-Crick complementarity rules,

b) targets *Shigella sonnei* consisting of a fragment greater than 10 to 40 bases in length of a nucleotide sequence SEQ ID NO: 4, an RNA equivalent thereof, or a nucleic acid complementary to said molecule, capable of base-pairing according to the standard Watson-Crick complementarity rules,

c) targets *Shigella dysenteriae* consisting of a fragment greater than 10 to 40 bases in length of a nucleotide sequence SEQ ID NO: 5, an RNA equivalent thereof, or a nucleic acid complementary to said molecule, capable of base-pairing according to the standard Watson-Crick complementarity rules,

or

d) targets *Shigella boydii* consisting of a fragment greater than 10 to 40 bases in length of a nucleotide sequence SEQThe EP '606 patent does not provide a disclosure of a layer which is derived from an ethylene-vinyl alcohol copolymer such EVOH (our study of the EP is based on CA 2,048,704). Thus, the EP is not, in and of itself, effective as an antrepation against any of the TI claims.

ID NO: 6, an RNA equivalent thereof, or a nucleic acid complementary to said molecule, capable of base-pairing according to the standard Watson-Crick complementarity rules.

57. (Currently Amended) A probe as in claim 55 which comprises 15-25 bases in length.

58. (Currently Amended) A probe as in claim 56 which comprises 15-25 bases in length.

Exhibit B

UNIVERSITY OF MARYLAND
OFFICE OF TECHNOLOGY COMMERCIALIZATION
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MEMORANDUM

TO: Dr. Anwarul Huq
Dr. Afzal Chowdhury
Dr. Rita Colwell

FROM: James Poulos
Executive Director

RE: Nucleic Acid Compositions for Differentiating Shigella Strains
University of Maryland Reference: LS-97-046

DATE: May 17, 2001

Thank you for submitting the above-referenced invention disclosure. As you know, it is OTC's usual practice to evaluate the commercial potential of submitted disclosures by contacting industrial representatives. After filing an initial U.S. provisional patent application on February 20, 1997 and a US Patent Application (09,027,439) on February 20, 1998, we marketed the invention to selected companies in the field. It was also made available for review by linking to our home page from web sites such as National Technology Transfer Center, Knowledge Express, the Association of University Technology Managers, and others.

By agreement, (MIPS No. 1206.25) we will transfer University rights to the joint owner, Cabtech, Inc.

Please be advised that the University will not take any further action regarding this case. If you so desire, you are free to proceed with the referenced US Patent Application, in partnership with Cabtech, at your own expense.

This action, however, is not intended to waive future University interests if further development of the invention makes use of University time, facilities, or resources.

Please contact me if you have any questions. We look forward to working with you on future projects.

cc: Dr. William Straube
Dr. Frank Portugal
Mr. Lou Robinson
Megan Michael
Nancy Gebhart